

## REMARKS

### **Information Disclosure Statement**

Contrary to the indication at page 5 of the Office Action, noting that the references cited in the International Search Report were not listed on a PTO Form-1449 form, an IDS was filed with the PTO on April 10, 2002. A copy of the filed IDS (PTO Form-1449) is attached for purposes of clarifying the record.

Applicants have elected Group I, claims 1-19. Claims 20-28 are cancelled without prejudice or disclaimer. Applicants reserve the right to file subsequent divisional or continuation applications to cover any unclaimed subject matter.

### **Rejection of the Claims Under 35 U.S.C. §112, second paragraph**

Claims 2-19 have been rewritten to correct any typographical errors and to put the claims in proper US format. The Claims have not been amended for any reason related to patentability and the scope of the claims remains unchanged.

In claim 15, choice (a) option indicates that the hydrocarbon chain has 2-4 carbon atoms, not 4-6 as indicated in the office action at page 3.

In claim 16, at line 14, "acyl" refers to the residue R-C(O)-. The C<sub>1</sub>- C<sub>8</sub> acyl group refers to a chain of 1 to 8 carbon atoms attached to the -C(O)- group.

In claim 19, "complex acid" is a term of art which is readily understood by those of ordinary skill in the chemical arts, see e.g. Haackes Chemical Dictionary.

**Rejection of the Claims Under 35 U.S.C. §102(b)**

Claims 1-6, 8-11 and 13 stand rejected for allegedly being anticipated by Boyle. Applicants respectfully traverse for the reasons discussed below.

Boyle discloses the hydrogenation of folic acid by adding a solution of folic acid on NaOH, adjusted to pH 7 with HCl, to a catalyst solution obtained in stirring (Pyridin)<sub>3</sub>RhCl<sub>3</sub> with (+) or (-)-N-1-phenylethylformamide and NaBH<sub>4</sub> under hydrogen. Boyle uses monodentate carboxylic acid amides as ligands.

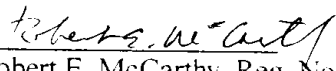
Thus, Boyle does not disclose a process for the preparation of tetrahydropterin and tetrahydropterin derivatives by the hydrogenation of pterin and pterin derivatives with hydrogen in the presence of a hydrogenation catalyst with ligands comprising tertiary phosphines, or comprising bidentate ligands with tertiary amine group and a phosphine group or with two tertiary phosphine groups as complexing groups, whereby the bidentate ligands form together with the metal atom a five- to ten membered ring.

In view of the significant difference in the ligands between Boyle and the instant invention, there is clearly no anticipation under §102(b). In order to have a proper rejection based on anticipation, all material elements must be found in one prior art source, *In re Marshall* (CCPA 1978), 577 F.2d 301, 198 USPQ 344. Therefore, the §102(b) rejection is clearly improper and should be withdrawn.

In view of the amendments and above remarks, favorable consideration is courteously requested. However, if there are any remaining issue(s), the Examiner is cordially invited to telephone the undersigned at the number indicated below.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The pages are captioned "Version With Markings to Show Changes Made".

Respectfully submitted.

  
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Version With Markings to Show Changes Made

**IN THE CLAIMS :**

Please **amend** the claims as follows:

1. (Amended) A process ~~Process~~ for the preparation of tetrahydropterin and tetrahydropterin derivatives by the hydrogenation of pterin and pterin derivatives with hydrogen in the presence of a hydrogenation catalyst, ~~characterized in that~~ wherein the hydrogenation is carried out in a polar reaction medium and metal complexes that are soluble in the reaction medium are used as the hydrogenation catalysts with ligands comprising tertiary phosphines, or comprising bidentate ligands with a tertiary amine group and a phosphine group or with two tertiary phosphine groups as complexing groups, whereby the bidentate ligands form together with a metal atom a five- to ten membered ring.

2. (Amended) The process ~~Process~~ according to claim 1, ~~characterised in that~~ wherein the polar reaction medium is an aqueous or alcoholic reaction medium.

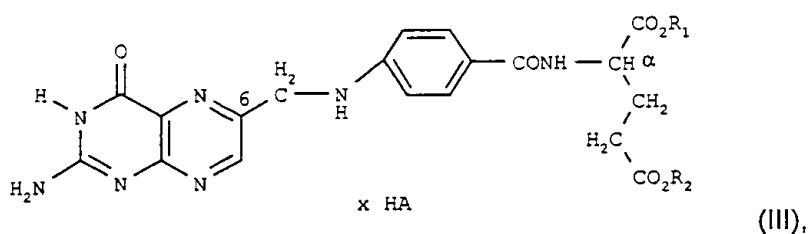
3. (Amended) The process ~~Process~~ according to claim 1, ~~characterized in that~~ wherein the pterin derivatives used are folic acid, folic acid salts, folic acid esters, folic acid ester salts or ~~dihydroforms~~ dihydro forms thereof for hydrogenation with hydrogen in the presence of a hydrogenation catalyst, the hydrogenation carried out at elevated pressure in the presence of metal complexes dissolved in the reaction medium as

hydrogenation catalysts, with the proviso that in the event of using folic acid, carboxylic acids thereof or ~~dihydroforms~~ dihydro forms thereof the reaction medium is aqueous, and in the event of using folic acid esters, folic acid ester salts or ~~dihydroforms~~ dihydro forms thereof the reaction medium is an alcohol.

4. (Amended) ~~The process~~ Process according to claim 1 for the asymmetric hydrogenation of prochiral pterin derivatives with hydrogen in the presence of a hydrogenation catalyst, ~~characterized in that~~ wherein the hydrogenation is carried out in a polar reaction medium and metal complexes that are soluble in the reaction medium are used as the hydrogenation catalysts, the metal complexes containing chiral ligands.

5. (Amended) ~~The process~~ Process according to claim 4 for the asymmetric hydrogenation of folic acid, folic acid salts, folic acid esters, folic acid ester salts or ~~dihydroforms~~ dihydro forms thereof as pterin derivatives, with hydrogen in the presence of a hydrogenation catalyst, ~~characterized in that~~ wherein the hydrogenation is carried out at elevated pressure in the presence of metal complexes dissolved in the reaction medium as hydrogenation catalysts, the metal complexes containing chiral ligands, with the proviso that where folic acid, carboxylic acid salts thereof or ~~dihydroforms~~ dihydro forms are used, that the reaction medium is aqueous, and where folic acid esters, folic acid ester salts or ~~dihydroforms~~ dihydro forms thereof are used, the reaction medium is an alcohol.

6. (Amended) The process ~~Process~~ according to claim 5, characterized in that wherein the folic acid ester salts satisfy formula III and are in the form of their enantiomers or mixtures,



in which  $R_1$  or  $R_2$  is H, ~~and  $R_2$  or  $R_1$ , or both  $R_1$  and  $R_2$  independently of one another~~ and one of  $R_1$  or  $R_2$  or both  $R_1$  and  $R_2$  independently of one another represent a monovalent hydrocarbon radical or a ~~heterohydrocarbon~~ radical attached via a carbon atom, with heteroatoms selected from the group comprising -O-, -S-, and -N-, HA stands for a monobasic to tribasic inorganic or organic acid, and x denotes an integer from 1 to 6 or a fractional number between 0 and 6.

7. (Amended) The process ~~Process~~ according to claim 6, characterized in that wherein the acid HA in formula III is unsubstituted or substituted phenylsulphonic acid.

8. (Amended) The process ~~Process~~ according to claim 1, ~~characterized in that~~  
wherein said process it is carried out at a hydrogen pressure of 1 to 500 bars.

9. (Amended) The process ~~Process~~ according to claim 1, ~~characterized in that~~  
wherein the temperature is 0 to 150<sup>0</sup> C.

10. (Amended) The process ~~Process~~ according to claim 1, ~~characterized in that~~  
wherein the molar ratio of substrate to catalyst is 10 to 100,000.

11. (Amended) The process ~~Process~~ according to claim 1, ~~characterized in that~~  
wherein the aqueous reaction medium is water or water in admixture with an organic  
solvent.

12. (Amended) The process ~~Process~~ according to claim 2 ~~1~~, ~~characterized in that~~  
wherein the alcoholic reaction medium is an alcohol, or an alcohol in admixture with an  
organic solvent.

13. (Amended) The process ~~Process~~ according to claim 1, ~~characterized in that~~  
wherein the metal complexes contain a d-8 metal, ~~preferably~~ comprising iridium,  
rhodium or ruthenium.

14. (Amended) The process ~~Process~~ according to claim 1, ~~characterized in that~~  
wherein the metal complex contains achiral or chiral ditertiary diphosphines as ligand.

15. (Amended) The process according to claim 14, wherein the ditertiary diphosphines for an alcoholic reaction medium are ones in which the phosphine groups are attached (a) to various carbon atoms of a hydrocarbon chain having 2 to 4 carbon atoms, or (b) directly via a bridging group  $-\text{CR}_a\text{R}_b-$  in the ortho positions of a cyclopentadienyl ring or to a cyclopentadienyl ring of a ferrocenyl, where  $\text{R}_a$  and  $\text{R}_b$  are the same or different and stand for H,  $\text{C}_1\text{-C}_8$  alkyl,  $\text{C}_1\text{-C}_4$  fluoroalkyl,  $\text{C}_5\text{-C}_6$  cycloalkyl, phenyl, benzyl, or phenyl or benzyl substituted with 1 to 3  $\text{C}_1\text{-C}_4$  alkyl or  $\text{C}_1\text{-C}_4$  alkoxy.

16. (Amended) The process according to claim 14, wherein the diphosphines which can be used in an alcoholic reaction medium satisfy formula IV,

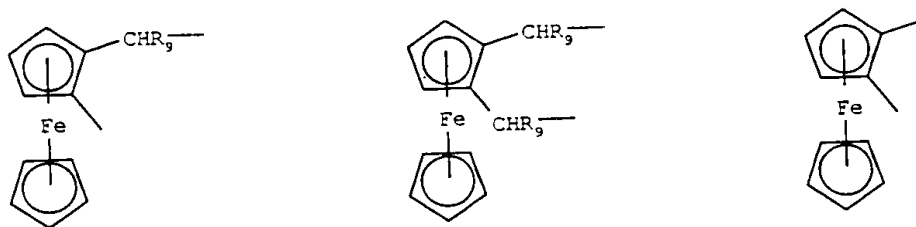


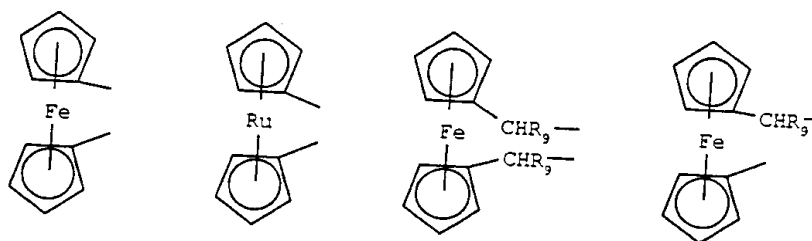
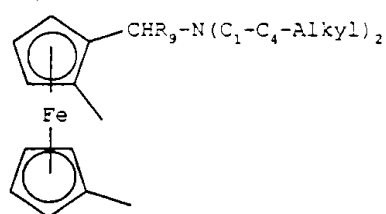
in which

$\text{R}_4$ ,  $\text{R}_5$ ,  $\text{R}_7$  and  $\text{R}_8$  independently of one another represent a hydrocarbon radical with 1 to 20 carbon atoms, which is unsubstituted or substituted with halogen,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  haloalkyl,  $\text{C}_1\text{-C}_6$  alkoxy,  $\text{C}_1\text{-C}_6$  haloalkoxy,  $(\text{C}_6\text{H}_5)_3\text{Si}$ ,  $(\text{C}_1\text{-C}_{12} \text{ alkyl})_3\text{Si}$ ,  $-\text{NH}_2$ ,  $-\text{NH}(\text{C}_1\text{-C}_{12} \text{ alkyl})$ ,  $-\text{NH}(\text{phenyl})$ ,  $-\text{NH}(\text{benzyl})$ ,  $-\text{N}(\text{C}_1\text{-C}_{12} \text{ alkyl})_2$ ,  $-\text{N}(\text{phenyl})_2$ ,  $-\text{N}(\text{benzyl})_2$ , morpholinyl, piperidinyl, pyrrolidinyl, piperazinyl,  $-\text{ammonium-X}_3^-$ ,  $-\text{SO}_3\text{M}_1$ ,  $-\text{CO}_2\text{M}_1$ ,  $-\text{PO}_3\text{M}_1$  or  $-\text{CO}_2\text{-C}_1\text{-C}_6 \text{ alkyl}$ , in which  $\text{M}_1$  represents an alkali metal or hydrogen and  $\text{X}_3^-$  is the anion of a monobasic acid; or  $\text{R}_4$  and  $\text{R}_5$ , and  $\text{R}_7$  and  $\text{R}_8$



respectively together denote tetramethylene, pentamethylene, or 3-oxa-pentane-1,5-diyl, unsubstituted or substituted with halogen, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkoxy; and R<sub>6</sub> is C<sub>2</sub>-C<sub>4</sub> alkylene, unsubstituted or substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>5</sub> or C<sub>6</sub> cycloalkyl, phenyl, naphthyl, or benzyl; 1,2- or 1,3-cycloalkylene, 1,2- or 1,3-cycloalkenylenylene, 1,2- or 1,3-bicycloalkylene or 1,2- or 1,3-bicycloalkenylenylene with 4 to 10 carbon atoms, unsubstituted or substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, or benzyl; 1,2- or 1,3-cycloalkylene, 1,2- or 1,3-cycloalkylene, 1,2- or 1,3-bicycloalkylene or 1,2- or 1,3-bicycloalkylene with 4 to 10 carbon atoms, unsubstituted or substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, or benzyl, at whose 1 and/or 2 positions or at whose 3-position methylene or C<sub>2</sub>-C<sub>4</sub> alkylidene is attached; 1,4-butylene substituted in the 2,3 positions with R<sub>9</sub>R<sub>10</sub> C(O)-<sub>2</sub>, and which in the 1 and/or 4 positions is unsubstituted or substituted with C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, or benzyl, and where R<sub>9</sub> and R<sub>10</sub> independently of one another represent hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl or benzyl; 3,4- or 2,4-pyrrolidinylene or methylene-4-pyrrolidine-4-yl whose nitrogen atom is substituted with hydrogen, C<sub>1</sub>-C<sub>12</sub> alkyl, phenyl, benzyl, C<sub>1</sub>-C<sub>12</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>8</sub> acyl, C<sub>1</sub>-C<sub>12</sub> alkylaminocarbonyl; or denotes 1,2-phenylene, 2-benzylene, 1,2-xylylene, 1,8-naphthylene, 2,2'-dinaphthylene or 2,2'-diphenylene, unsubstituted or substituted with halogen, -OH, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, phenyl, benzyl, phenyloxy or benzyloxy; or R<sub>6</sub> stands for a radical of the formulas

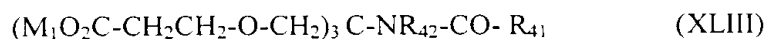




in which  $R_9$  denotes hydrogen,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_4$  fluoroalkyl, unsubstituted phenyl or phenyl substituted with 1 to 3F, Cl, Br,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy or fluoromethyl.

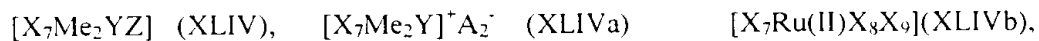
17. (Amended) The process according to claim 14, wherein diphosphines for an aqueous reaction medium are ones that contain one or more water-solubilising polar substituents, which are attached either direct or via a bridging group to substituents of the phosphine groups.

18. (Amended) The process according to claim 17, wherein the diphosphines for an aqueous reaction medium are ones of formula XLIII.



in which  $M_1$ , stands for H, an alkali metal cation or an ammonium cation,  $R_{42}$  denotes  $C_1$ - $C_4$  alkyl and preferably H, and  $R_{41}$  is the monovalent radical of a chiral diteritary diphosphine, with the CO group being attached direct to a carbon or nitrogen atom of the diphosphine skeleton, or to an oxygen or nitrogen atom or to a carbon atom of a bridging group of the diphosphine skeleton.

19. (Amended) The process ~~Process~~ according to claim 1, ~~characterized in that~~ wherein the hydrogenation catalysts are metal complexes of formulas XLIV, XLIVa and XLIVb,



in which

Y stands for monoolefin ligands or a diene ligand;

$X_7$  represents an achiral or chiral ditertiary diphosphine that forms a 5 to 7 membered ring with the metal atom  $Me_2$  or Ru;

$Me_2$  denotes Ir(I) or Rh(I);

Z represents  $-Cl$ ,  $-Br$ , or  $-I$ ; and

$A_2$  is the anion of an oxy-acid or complex acid;

$X_8$  and  $X_9$  are the same or different and have the meaning of Z and  $A_2$ , or  $X_8$ , and

$X_9$  stands for allyl or 2-methylallyl, or  $X_8$  has the meaning of Z or A and  $X_9$  stands for hydride.